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Association of Hormonal Contraception With Depression

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IMPORTANCE Millions of women worldwide use hormonal contraception. Despite the clinical evidence of an influence of hormonal contraception on some women's mood, associations between the use of hormonal contraception and mood disturbances remain inadequately addressed.

OBJECTIVE To investigate whether the use of hormonal contraception is positively associated with subsequent use of antidepressants and a diagnosis of depression at a psychiatric hospital.

DESIGN, SETTING, AND PARTICIPANTS This nationwide prospective cohort study combined data from the National Prescription Register and the Psychiatric Central Research Register in Denmark. All women and adolescents aged 15 to 34 years who were living in Denmark were followed up from January 1, 2000, to December 2013, if they had no prior depression diagnosis, redeemed prescription for antidepressants, other major psychiatric diagnosis, cancer, venous thrombosis, or infertility treatment. Data were collected from January 1, 1995, to December 31, 2013, and analyzed from January 1, 2015, through April 1, 2016.

EXPOSURES Use of different types of hormonal contraception.

MAIN OUTCOMES AND MEASURES With time-varying covariates, adjusted incidence rate ratios (RRs) were calculated for first use of an antidepressant and first diagnosis of depression at a psychiatric hospital.

RESULTS A total of 1 061 997 women (mean [SD] age, 24.4 [0.001] years; mean [SD] follow-up, 6.4 [0.004] years) were included in the analysis. Compared with nonusers, users of combined oral contraceptives had an RR of first use of an antidepressant of 1.23 (95% CI, 1.22-1.25). Users of progestogen-only pills had an RR for first use of an antidepressant of 1.34 (95% CI, 1.27-1.40); users of a patch (norgestrolmin), 2.0 (95% CI, 1.76-2.18); users of a vaginal ring (etonogestrel), 1.6 (95% CI, 1.55-1.69); and users of a levonorgestrel intrauterine system, 1.4 (95% CI, 1.31-1.42). For depression diagnoses, similar or slightly lower estimates were found. The relative risks generally decreased with increasing age. Adolescents (age range, 15-19 years) using combined oral contraceptives had an RR of a first use of an antidepressant of 1.8 (95% CI, 1.75-1.84) and those using progestin-only pills, 2.2 (95% CI, 1.99-2.52). Six months after starting use of hormonal contraceptives, the RR of antidepressant use peaked at 1.4 (95% CI, 1.34-1.46). When the reference group was changed to those who never used hormonal contraception, the RR estimates for users of combined oral contraceptives increased to 1.7 (95% CI, 1.66-1.71).

CONCLUSIONS AND RELEVANCE Use of hormonal contraception, especially among adolescents, was associated with subsequent use of antidepressants and a first diagnosis of depression, suggesting depression as a potential adverse effect of hormonal contraceptive use.

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Depression is associated with a substantial burden in developed and developing countries.[1] The lifetime prevalence of depression is about twice as high in women as in men across different populations.[2-5] Nevertheless, before puberty, girls are found to be equally or less depressed than boys.[6,7] The 2 female sex hormones—estrogen and progesterone—have been hypothesized to play a role in the cause of depressive symptoms.[8-12] In a recent review, Toffoletto et al[13] found initial evidence that sex steroid hormones have an influence on the cortical and subcortical regions implicated in emotional and cognitive processing. Gingnell et al[14] found that use of combined oral contraceptives among women who previously had experienced emotional adverse effects resulted in mood deterioration and changes in emotional brain reactivity. The addition of progesterone to hormone therapy has been shown to induce adverse mood effects in women.[15,16] Likely mechanisms also include the action of progesterone metabolites on the γ-aminobutyric acid A receptor complex, which is the major inhibitory system in the human central nervous system.[17] Levels of neuroactive metabolites of progesterone increase during the luteal phase of the menstrual cycle in fertile women, and some experience negative mood symptoms.[17] Moreover, external progestins, probably more than natural progesterone, increase levels of monoamine oxidase, which degrades serotonin concentrations and thus potentially produces depression and irritability.[18] Clinical studies have indicated that changes in estrogen levels may trigger depressive episodes among women at risk for depression[19] and that women with major depression generally have lower estradiol levels than do control individuals.[20] Freeman et al[21] found that women with a faster transition to menopause followed by stable hormone levels had fewer depressive symptoms. In a recent double-blind placebo-controlled study,[22] women were randomized to sex hormone manipulation with groserelin (gonadotropin-releasing hormone agonist) implant or placebo, which triggered subclinical depressive symptoms in the intervention group. The depressive symptoms were positively associated with the net decrease in estradiol levels.

Few studies have quantified the effect of modern low-dose hormonal contraceptive use on the risk for depression.[23-28] Two studies[24-26] found teenage users of progestin-only contraception to be more frequent users of antidepressants than nonusers of hormonal contraceptives. One study[23] found no association between oral contraceptive use and mood symptoms, and 3 studies[25,27,28] suggested that the use of hormonal contraception was associated with better mood. We found few prior studies that assessed the effect of hormonal contraceptives on the risk for subsequent depression in a prospective cohort design and none that took into account the temporality between use of hormonal contraceptives and development of depression.

Because mood symptoms are a known reason for cessation of hormonal contraceptive use,[29-31] cross-sectional studies are vulnerable to healthy-user bias causing underestimation of a possible influence on depression. Because hormonal contraception introduces synthetic hormones and modulates the internal hormone production, an examination of the influence of hormonal contraceptives on women's mood is warranted. The aim of this study was to assess the influence of specific types of hormonal contraceptives on the risk for first use of antidepressants and first diagnosis of depression as an inpatient or an outpatient at a psychiatric hospital.

Key Points

Question Is use of hormonal contraception associated with treatment of depression?

Findings In a nationwide prospective cohort study of more than 1 million women living in Denmark, an increased risk for first use of an antidepressant and first diagnosis of depression was found among users of different types of hormonal contraception, with the highest rates among adolescents.

Meaning Health care professionals should be aware of this relatively hitherto unnoticed adverse effect of hormonal contraception.

Methods

Study Population

The Danish Sex Hormone Register Study[32] is an ongoing nationwide cohort study that includes all women living in Denmark. The cohort was identified by the unique personal identification number given to all Danish citizens at birth or immigration. This number is used in all public registers, allowing reliable linkage of data between registers. The databases were available through Statistics Denmark, and approval for their use was obtained from the Danish Data Protection Agency, which also determined that informed consent was not required because the study used deidentified data from large databases.

In the present study, we observed adolescents and women aged 15 to 34 years (hereinafter referred to as women) at any time during the 14 years from January 1, 2000, to December 31, 2013, and in the previous 5-year period. To ensure that incident events of depression were identified, all women with a depression diagnosis or use of antidepressants before January 1, 2000, or before their 15th birthday were excluded, as were all women with other major psychiatric diagnoses using the following codes from the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*: organic, DF0*; manic episode, DF30; bipolar affective disorder, DF31*; schizophrenia, DF2*; and mental retardation, DF7*. To exclude women with contraindications against the use of hormonal contraceptives, women with a diagnosis of cancer or venous thrombosis or who underwent treatment for infertility before study entry were excluded. The National Health Register provided data on discharge diagnoses of cancer and venous thrombosis since 1977, and the Psychiatric Central Research Register provided data on psychiatric diagnoses for all inpatients and outpatients since 1995. Infertility was defined as having a redeemed prescription of ovarian-stimulating drugs (Anatomical Therapeutic Chemical classification system code MG03G in the National Prescription Register). Daily updated information on immigration, emigration, and death was obtained from Statistics Denmark. Women immigrating after 1995

were excluded to ensure information on prior depression and other censoring variables for at least 5 years before study entry. The National Birth Register provided information on births since 1973 (eFigure 1 in the Supplement).

Hormonal Contraception

The National Prescription Register provided individual exposure information on prescribed and redeemed medication from all Danish pharmacies since 1995 and was categorized according to estrogen type and dose, progestin type, and route of administration (eTable 1 in the Supplement). Use of hormonal contraception was modeled as time-varying covariates, with information updated daily. All prescriptions were extended with 28 days or less if a new prescription was redeemed.[33] Hormone use was defined as current or recent use (cessation within the previous 6 months) to ensure that women who quit hormonal contraceptive use owing to depression but before any treatment was initiated were considered exposed to hormonal contraceptives. The reference group consisted of nonusers, defined as those who never used hormonal contraceptives plus former users.

Depression

Two outcome measures for incident depression were addressed. First, a first redeemed prescription of an antidepressant was recorded in the National Prescription Register (eTable 2 in the Supplement). The National Prescription Register covers all redeemed prescriptions of antidepressants from Danish pharmacies, including 98.7% of all antidepressants used in Denmark. The second outcome was a first discharge diagnosis of depression from the Psychiatric Central Research Register, defined by codes F32 to F33.9 from the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*. This outcome included all inpatients and outpatients at psychiatric departments in Denmark since 1995.

Covariates

Statistics Denmark delivered data for all women on age, length of schooling, and ongoing or completed educational level (unknown, elementary school only, high school only, skilled worker, theoretical education, and theoretical education with research qualifications). Diagnoses of polycystic ovary syndrome and endometriosis were obtained from the National Health Register. The National Birth Register provided information on body mass index (calculated as weight in kilograms divided by height in meters squared) (by categories of <18.5, 18.5-25.0, >25.0 to 30.0, and >30.0) since 2004 and smoking habits (yes or no) since 1991 for all women who had been pregnant.

Statistical Analysis

All women in the study population were followed up from entry (January 1, 2000, or 15th birthday) and until event, emigration, death, or the end of follow-up on December 31, 2013, whichever came first. Women were censored during the study period for the same reasons as the primary exclusions and temporarily during pregnancy and 6 months after delivery. To account for age and time trends in depression, we adjusted for calendar year and age using 1-year bands. We also adjusted for educational level, polycystic ovary syndrome, and endometriosis. Incidence rate ratios (RRs) and 95% CIs were calculated using Poisson regression.

Among women starting hormonal contraceptive use in the study period, we assessed the effect of duration of use compared with nonusers. Among parous women, an additional sensitivity analysis adjusted for smoking and body mass index. In 2 additional analyses, RRs among users of different hormonal contraception product types were calculated, with users of a combination of ethinyl estradiol, 30 to 40 µg, and levonorgestrel as the reference group or with those who never used hormonal contraceptives as the reference group.

Finally, sensitivity analyses were conducted on the subcohort of women who started hormonal contraceptive use sometime during the study period. Each woman contributed to the exposed and unexposed observation time. Among women who started use of hormonal contraceptives, incidence rates within 1 year after initiation of hormonal contraception were compared with the incidence rate during the time before the initiation of hormonal contraceptive use. We thereby controlled for all potential confounders, which did not change during the observation period and eliminated healthy-user bias.

Results

The study population included 1 061 997 women (mean [SD] age, 24.4 [0.001] years; mean [SD] follow-up, 6.4 [0.004] years) and 6 832 938 person-years of observation during the study period. During follow-up, 55.5% of women were current or recent users of hormonal contraception. Use of hormonal contraception according to age in 2013 is illustrated in eFigure 2 in the Supplement. Within the first year of hormonal contraceptive use, 0.04% of women changed to another product and 10% ceased using their product. A total of 133 178 first prescriptions of antidepressants and 23 077 first diagnoses of depression were detected during follow-up. Data were analyzed from January 1, 2015, through April 1, 2016.

Characteristics of Users of Hormonal Contraception

Women using hormonal contraception were a mean (SD) of 24.3 (0.01) years of age; nonusers were a mean (SD) of 24.4 (0.01) years of age. Users of the levonorgestrel intrauterine system were a mean (SD) of 31 (0.05) years of age. Women using 50 µg of combined oral contraceptives, implants, or medroxyprogesterone acetate depot were more likely to have a lower educational level than were women using other types of hormonal contraception. That tendency was most pronounced for women using medroxyprogesterone acetate depot (Table 1).

Hormonal Contraception and Depression

Among all users of hormonal contraceptives, the crude incidence rate of first use of antidepressants was 2.2 per 100 person-years; that of first diagnosis of depression at a psychiatric hospital, 0.3 per 100 person-years. The corresponding crude incidence rates in nonusers of hormonal contraception were 1.7 and 0.28 per 100 person-years, respectively.

Table 1. Characteristics of Users of Different Types of Hormonal Contraception[a]

Type of Hormonal Contraception	Year	Person-years	Age, Mean (SD), y	% of Women			
				Educational Level			
				Short[b]	Long[c]	PCOS	Endometriosis
Nonuse	NA	3 041 595	24.4 (0.01)	8.2	4.4	0.9	1.1
All use	NA	3 791 343	24.3 (0.01)	6.9	6.5	1	1.3
Combined products							
Oral							
Ethinyl estradiol, 50 µg							
Norethisterone	1995-2002	8060	26.3 (0.1)	17.0	2.7	1.2	2.2
Levonorgestrel	1995-2009	14 197	26.2 (0.1)	14.7	2.8	1.4	3.8
Ethinyl estradiol, 30-40 µg							
Norethisterone	1995→	38 927	25.1 (0.1)	10.6	4.4	1.0	1.5
Levonorgestrel	1995→	280 445	24.5 (0.02)	6.2	5.9	0.5	0.9
Norgestimate	1995→	339 501	24.5 (0.02)	7.2	6.6	0.9	1.1
Desogestrel	1995→	170 544	25.6 (0.03)	8.7	6.4	1.1	2.0
Gestodene	1995→	757 337	25.4 (0.01)	7.6	6.7	0.8	1.8
Drospirenone	2001→	327 930	23.4 (0.02)	6.6	7.2	1.5	1.3
Cyproterone acetate	1995→	159 931	24.1 (0.03)	6.1	8.5	3.0	1.2
Ethinyl estradiol, 20 µg							
Desogestrel	1995→	659 847	23.5 (0.01)	6.5	6.6	0.8	1.3
Gestodene	1997→	693 013	22.9 (0.01)	6.2	6.0	0.8	1.1
Drospirenone	2006→	64 894	22.2 (0.04)	4.6	7.7	1.3	0.5
Natural estrogen							
Dienogest	2009→	3711	24.1 (0.2)	4.0	8.0	1.4	2.0
Nonoral							
Patch (norgestrolmin)	2003→	8081	23.5 (0.1)	11.5	3.5	1.2	1.4
Vaginal ring (etonogestrel)	2002→	69 605	25.1 (0.04)	5.9	10.4	0.8	1.1
Progestin-only products							
Oral							
Norethisterone	1995→	33 182	27.6 (0.1)	5.2	7.4	0.7	1.4
Levonorgestrel	1995-2005	1289	28.3 (0.3)	5.4	9.8	0.7	1.7
Desogestrel	2001→	40 069	26.3 (0.1)	4.5	7.5	0.7	1.6
Nonoral							
Implant	1999→	28 867	23.0 (0.1)	16.6	1.8	0.7	0.8
Levonorgestrel IUS	1995→	81 281	31.0 (0.1)	3.8	3.5	0.5	1.5
Medroxyprogesterone acetate depot	1995→	10 587	22.7 (0.1)	26.4	0.4	1	0.7

Abbreviations: IUS, intrauterine system; PCOS, polycystic ovary syndrome; →, study end (2013).

[a] Includes 1 061 997 women aged 15 to 34 years.

[b] Indicates basic school.

[c] Indicates postgraduate degree.

Compared with nonusers, users of combined oral contraceptives experienced an RR of a first use of antidepressants of 1.2 (95% CI, 1.22 to 1.25). Women using progestin-only pills had an RR of 1.3 (95% CI, 1.27-1.40); a transdermal patch (norgestrolmin), 2.0 (95% CI, 1.76-2.18); a vaginal ring (etonogestrel), 1.6 (95% CI, 1.55-1.69); an implant, 2.1 (95% CI, 2.01-2.24); a levonorgestrel intrauterine system, 1.4 (95% CI, 1.31-1.42); and medroxyprogesterone acetate depot, 2.7 (95% CI, 2.45-2.87). The RRs of a first diagnosis of depression were slightly lower or similar (Table 2).

Age-stratified analyses demonstrated decreasing RRs of a first use of antidepressants with increasing age for the most commonly used products (Figure 1). Analyses restricted to adolescents (aged 15-19 years) showed notably higher RRs of first use of antidepressants and first diagnosis of depression. Compared with nonusers, users of combined oral contraceptives experienced a 1.8-fold higher rate (95% CI, 1.75-1.84) of first use of antidepressants; users of progestin-only pills experienced a 2.2-fold higher rate (95% CI, 1.99-2.52). Nonoral products implied a 3-fold increased risk for first use of antidepressants. The RRs for a first diagnosis of depression at a psychiatric hospital were similar or slightly lower (Table 3).

Assessment of the association between the duration of use and the risk for first use of antidepressants demonstrated increasing relative risks with length of use. For use of hormonal contraceptives of less than 1 month, RRs were 1.1 (95% CI, 0.95-1.15) for first use of antidepressants and 1.2 (95% CI, 1.00-1.44) for first diagnosis of depression; for 1 to less than 2

Table 2. Rate Ratio of First Use of Antidepressants and First Diagnosis of Depression in All Women[a]

		First Use of Antidepressants			First Diagnosis of Depression		
Type of Hormonal Contraception	Person-years	No. of Events	RR[b]	RR (95% CI)[c]	No. of Events	RR[b]	RR (95% CI)[c]
Nonuse	3 041 595	50 346	1	1 [Reference]	9310	1	1 [Reference]
All oral combined	3 518 381	74 126	1.2[d]	1.2 (1.22-1.25)[d]	12 211	1.0[d]	1.1 (1.08-1.14)[d]
All progestin-only	74 540	1884	1.3[d]	1.3 (1.27-1.40)[d]	296	1.1	1.2 (1.04-1.31)[d]
Combined products							
Oral							
Ethinyl estradiol, 50 µg							
Norethisterone	8060	176	1.5[d]	1.5 (1.26-1.69)[d]	22	1.3	1.2 (0.77-1.79)
Levonorgestrel	14 197	424	1.7[d]	1.6 (1.47-1.78)[d]	63	1.5[d]	1.4 (1.09-1.78)[d]
Ethinyl estradiol, 30-40 µg							
Norethisterone	38 927	583	1.0	1.1 (0.98-1.15)	77	0.9	0.9 (0.70-1.11)
Levonorgestrel	280 445	5618	1.2[d]	1.3 (1.22-1.29)[d]	1017	1.0	1.1 (1.02-1.17)[d]
Norgestimate	339 501	7017	1.1[d]	1.2 (1.18-1.24)[d]	1114	1.0	1.1 (1.00-1.14)[d]
Desogestrel	170 544	3918	1.3[d]	1.3 (1.27-1.35)[d]	604	1.1[d]	1.2 (1.07-1.27)[d]
Gestodene	757 337	15 759	1.2[d]	1.2 (1.18-1.23)[d]	2430	1.0	1.1 (1.03-1.13)[d]
Drospirenone	327 930	7843	1.3[d]	1.4 (1.34-1.41)[d]	1395	1.2[d]	1.3 (1.23-1.38)[d]
Cyproterone acetate	159 931	3914	1.3[d]	1.5 (1.43-1.52)[d]	638	1.2[d]	1.3 (1.17-1.38)[d]
Ethinyl estradiol, 20 µg							
Desogestrel	659 847	13 276	1.1[d]	1.2 (1.14-1.19)[d]	2199	1.0	1.1 (1.00-1.10)[d]
Gestodene	693 013	13 854	1.1[d]	1.2 (1.15-1.19)[d]	2314	1.0	1.1 (1.00-1.10)
Drospirenone	64 894	1623	1.2[d]	1.4 (1.31-1.44)[d]	309	1.2[d]	1.3 (1.15-1.44)[d]
Natural estrogen							
Dienogest	3711	119	1.7[d]	1.8 (1.49-2.14)[d]	29	1.8[d]	1.9 (1.31-2.72)[d]
Nonoral							
Patch (norgestrolmin)	8081	333	2.1[d]	2.0 (1.76-2.18)[d]	60	1.9[d]	1.7 (1.34-2.23)[d]
Vaginal ring (etonogestrel)	69 605	2195	1.5[d]	1.6 (1.55-1.69)[d]	421	1.5[d]	1.6 (1.45-1.77)[d]
Progestin-only products							
Oral							
Norethisterone	33 182	771	1.2[d]	1.3 (1.18-1.37)[d]	110	1.0	1.1 (0.88-1.29)
Levonorgestrel	1289	31	1.5[d]	1.7 (1.18-2.38)[d]	4	1.3	1.5 (0.54-3.86)
Desogestrel	40 069	1082	1.3[d]	1.4 (1.30-1.46)[d]	182	1.2[d]	1.2 (1.06-1.42)[d]
Nonoral							
Levonorgestrel IUS	81 281	2373	1.4[d]	1.4 (1.31-1.42)[d]	397	1.4[d]	1.4 (1.22-1.50)[d]

Abbreviations: IUS, intrauterine system; RR, incidence rate ratio.

[a] Includes 1 061 997 women aged 15 to 34 years.

[b] Adjusted for age and calendar year.

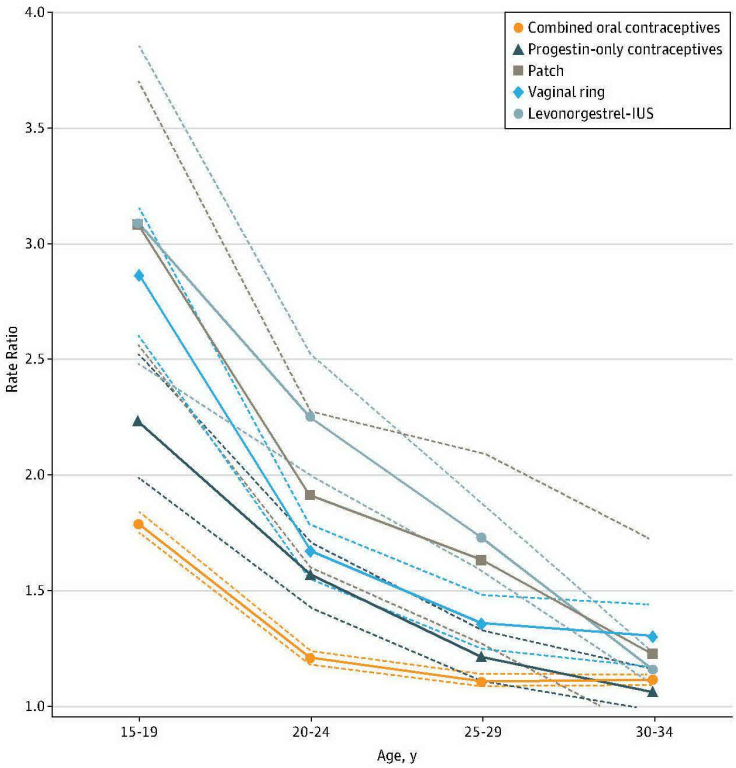
[c] Adjusted for age, calendar year, educational level, polycystic ovary syndrome, and endometrioses.

[d] Indicates statistical significance.

months, 1.1 (95% CI, 1.00-1.20) and 1.3 (95% CI, 1.07-1.54), respectively; and for 2 to less than 3 months, 1.4 (95% CI, 1.27-1.50) and 1.4 (95% CI, 1.14-1.62), respectively. Relative risks peaked after 6 months of use with an RR of 1.4 (95% CI, 1.34-1.46) for a first use of antidepressants and an RR of 1.5 (95% CI, 1.36-1.64) for a first diagnosis of depression. Thereafter relative risks decreased to RRs of 1.4 (95% CI, 1.32-1.41) and 1.4 (95% CI, 1.30-1.50), respectively, for use of 6 months to less than 1 year; 1.2 (95% CI, 1.21-1.26) and 1.2 (95% CI, 1.10-1.20), respectively, for use of 1 to less than 4 years; 1.1 (95% CI, 1.08-1.13) and 0.9 (95% CI, 0.87-0.97), respectively, for use of 4 to less than 7 years; and 1.0 (95% CI, 0.98-1.04) and 0.8 (95% CI, 0.77-0.88), respectively (unity), for use of 7 to less than 10 years (**Figure 2**).

When additionally adjusting for smoking and body mass index among parous women, the RR of first use of antidepressants did not change significantly for almost all products. An exception was the RR among women who used medroxyprogesterone acetate depot, which decreased from 2.4 (95% CI, 2.09-2.75) to 1.9 (95% CI, 1.65-2.16) with adjustment for confounders (eFigure 3 in the Supplement). When use of oral contraceptives that combined levonorgestrel and 30 to 40 µg of ethinyl estradiol constituted the reference group, a significantly higher rate of antidepressant use was found among women who used combined oral contraceptives with cyproterone acetate, natural estrogen with dienogest, and a patch or a vaginal ring (eTable 3 in the Supplement). When changing the reference group to those who never used hormonal contraceptives, all oral combined products conferred in all women an RR of 1.7 (95% CI, 1.66-1.71) for a first use of antidepressants and among adolescents an RR of 2.2 (95% CI, 2.18-2.31) (eTable 4 in the Supplement).

Figure 1. Rate Ratio of First Use of Antidepressants by Contraceptive Type



Includes all women in Denmark aged 15 to 34 years. Use of most types of hormonal contraceptives is compared with nonuse by participant age. IUS indicates intrauterine system.

Sensitivity Analyses on Starting Use of Hormonal Contraceptives

Compared with before use, the RR of antidepressant use 1 year after initiation of combined oral contraceptive use was 1.6 (95% CI, 1.58-1.69). Stratified by age groups, adolescents aged 15 to 19 years who started use of hormonal contraceptives had an RR of 1.8 (95% CI, 1.72-1.88). Women aged 20 to 30 years who started use of hormonal contraceptives had an RR of 1.4 (95% CI, 1.29-1.47) (eTable 5 in the Supplement).

Discussion

In this study, use of all types of hormonal contraceptives was positively associated with a subsequent use of antidepressants and a diagnosis of depression. That finding complies with the theory of progesterone involvement in the etiology of depression, because progestin dominates combined and progestin-only contraceptives. The high risk among women using the transdermal patch and vaginal ring compared with the corresponding pill is probably a question of dose rather than the route of administration.[34] Progestin-only products, including the levonorgestrel intrauterine system, also implied an increased risk for the use of antidepressants and a diagnosis of depression, supporting the finding that although the levonorgestrel intrauterine system primarily works locally, it also delivers levonorgestrel to the systemic circulation.[35] Adolescent women who used hormonal contraception experienced higher risks than women in general.

Strengths

Among the strengths of this study was the primarily nonselective inclusion of all adolescents and women aged 15 to 34 years living in Denmark and followed up for 14 years with no loss to follow-up and a study population of 1 million women. The information on the use of hormonal contraception and antidepressants was obtained through bar codes, eliminating recall bias. Women who used an antidepressant or had a diagnosis of depression before study entry were excluded. Next, women were temporarily censored during pregnancy and 6 months after delivery to reduce the influence of postpartum depression. Information on hormonal contraceptive use was updated daily and used as a time-varying covariate. Finally, we used alternative analysis strategies with 2 different outcomes and conducted a number of sensitivity analyses, all with consistent results.

Limitations

We do not expect general practitioners to be more likely to prescribe hormonal contraception to women at risk for depression because depression is mentioned in the leaflet as a possible adverse effect. Therefore, the opposite selection is more

Table 3. Rate Ratio of First Use of Antidepressants and First Diagnosis of Depression Among Adolescents[a]

	First Use of Antidepressants			First Diagnosis of Depression		
Type of Hormonal Contraception	Person-years	No. of Events	RR (95% CI)[b]	Person-years	No. of Events	RR (95% CI)[b]
Nonuse	1 094 654	10 257	1 [Reference]	1 106 800	2496	1 [Reference]
All oral combined	916 691	18 597	1.8 (1.75-1.84)[c]	943 325	3738	1.7 (1.63-1.81)
All progestin-only pills	10 277	287	2.2 (1.99-2.52)[c]	10 683	56	1.9 (1.49-2.53)[c]
Combined products						
Ethinyl estradiol, 50 µg						
Norethisterone	1120	22	2.6 (1.73-4.02)[c]	1137	2	1.2 (0.30-4.76)
Levonorgestrel	2042	56	2.4 (1.86-3.14)[c]	2126	10	2.2 (1.18-4.10)[c]
Oral						
Ethinyl estradiol, 30-40 µg						
Norethisterone	7735	78	1.4 (1.10-1.73)[c]	7830	17	1.5 (0.91-2.38)
Levonorgestrel	77 661	1507	1.7 (1.63-1.83)[c]	80 079	387	1.7 (1.51-1.91)[c]
Norgestimate	74 619	1559	1.9 (1.79-2.00)[c]	76 818	316	1.8 (1.61-2.05)[c]
Desogestrel	30 861	776	2.2 (2.02-2.34)[c]	32 017	143	2.0 (1.66-2.34)[c]
Gestodene	131 879	2842	1.9 (1.80-1.96)[c]	136 116	543	1.8 (1.60-1.94)[c]
Drospirenone	103 894	2174	1.9 (1.82-2.01)[c]	106 788	469	2.0 (1.85-2.27)[c]
Cyproterone acetate	38 339	834	2.0 (1.82-2.10)[c]	39 696	135	1.5 (1.27-1.80)[c]
Ethinyl estradiol, 20 µg						
Desogestrel	191 354	3720	1.7 (1.63-1.76)[c]	196 493	716	1.6 (1.46-1.74)[c]
Gestodene	228 840	4342	1.7 (1.63-1.76)[c]	234 863	859	1.6 (1.50-1.76)[c]
Drospirenone	27 244	659	1.8 (1.70-2.00)[c]	28 210	132	1.7 (1.44-2.06)[c]
Natural estrogen						
Dienogest	1093	27	2.0 (1.34-2.85)[c]	1142	9	2.6 (1.34-4.96)[c]
Nonoral						
Patch (norgestrolmin)	2526	115	3.1 (2.56-3.71)[c]	2705	23	2.8 (1.86-4.23)[c]
Vaginal ring (etonogestrel)	10 833	438	2.9 (2.60-3.16)[c]	11 513	85	2.7 (2.18-3.38)[c]
Progestin-only products						
Oral						
Norethisterone	3722	91	2.1 (1.67-2.52)[c]	3853	13	1.3 (0.76-2.27)
Desogestrel	6472	195	2.3 (2.03-2.69)[c]	6746	43	2.3 (1.68-3.08)[c]
Nonoral						
Levonorgestrel IUS	1627	80	3.1 (2.47-3.84)[c]	1832	20	3.2 (2.08-5.03)[c]

Abbreviations: IUS, intrauterine system; RR, incidence rate ratio.

[a] Includes participants aged 15 to 19 years.

[b] Adjusted for age, calendar year, educational level, polycystic ovary syndrome, and endometriosis.

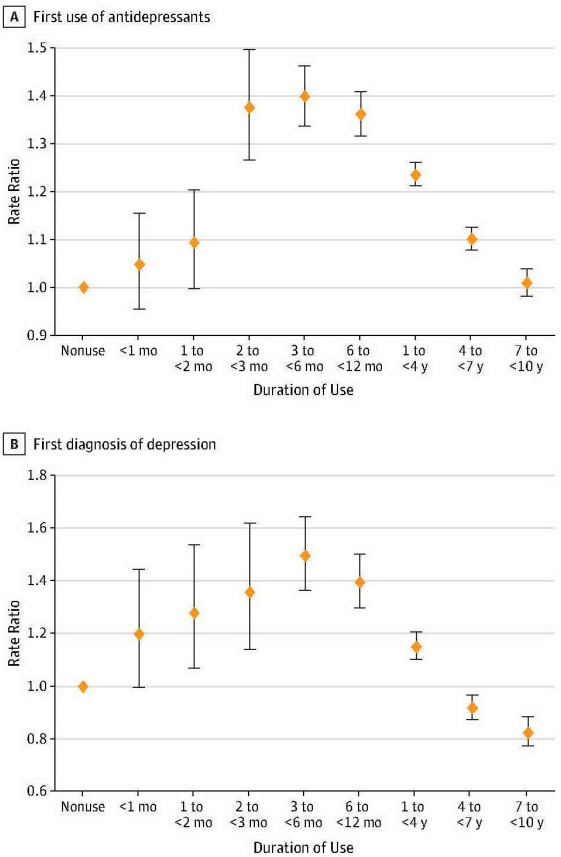
[c] Indicates statistical significance.

likely, implying a potential underestimation of the relative risks. We expect that institutionalized women and women with mental retardation or more severe psychiatric illness could be more likely to receive long-acting reversible contraceptive products such as medroxyprogesterone acetate depot or implants. Although we do not have a reference to support this concern, we decided to exclude these 2 specific products in the results tables because they might be influenced by confounding by indication. For the remaining products, these specific women account for a vanishing small fraction of all women using hormonal contraception. Thus, 80% of the female population in Denmark has used hormonal contraception some time during their reproductive life, which explains why women using hormonal contraceptives represent the general population of women in Denmark and not a selected subpopulation.

If prescribing physicians are more observant of the onset of depressive symptoms among patients to whom they have prescribed hormonal contraceptives, this could imply detection bias. Nevertheless, such bias likely cannot explain the increased risk for a first depression diagnosis at a psychiatric hospital because these diagnoses reflect the more severe depressive disorders that will be evident regardless of clinical attention. Moreover, if such a detection bias explains the increased risk, we would expect the risk estimates to be the same for all types of oral contraceptivs, which was not the case. Further, if such a detection bias was present in our data, we would expect higher risk estimates for redeemed prescriptions of antidepressants immediately after initiation of hormonal contraceptive use. However, the analyses of the duration of hormonal contraceptive use showed no significant increase in risk estimates until more than 2 months after initiation of hormonal contraceptive use.

A potential confounding factor might be the initiation of a sexual relationship because we speculate that this might

Figure 2. Rate Ratios of First Use of Antidepressants and First Diagnosis of Depression



Rate ratios are stratified by length of hormonal contraceptive use. Participants with any use of hormonal contraception were excluded at first pregnancy. Error bars indicate 95% CIs.

influence the risk for a first use of antidepressants and the diagnosis of depression. We therefore assessed the influence of sexual activity by restricting analyses to women who mostly (≥80%) have had their first intercourse (ages 20-30 years).[36] Results remained stable. Moreover, 80% of girls aged 11 to 15 years in Denmark used a condom at their first intercourse,[37] indicating that sexual relationships for many are likely to start before initiation of hormonal contraceptive use. Thus, many adolescents not using hormonal contraceptives are likely also to be sexually active. Therefore, sexual activity does not seem to be an important confounder for the association between the use of hormonal contraceptives and depression.

In a sensitivity analysis we aimed to eliminate the effect of all fixed confounders over time and attrition of susceptibility. Risk for antidepressant use 1 year after initiation of hormonal contraceptive use (disregarding discontinuation) was compared with the risk among the same women in the time before initiation of hormonal contraceptive use with adjustment for age and calendar year. This analysis found that the increased risk for first use of antidepressants was comparable with that found in the main analyses.

Our data indicate that adolescent girls are more sensitive than older women to the influence of hormonal contraceptive use on the risk for first use of antidepressants or first diagnosis of depression. This finding could be influenced by attrition of susceptibility, but also that adolescent girls are more vulnerable to risk factors for depression.[38]

We must consider that not all depressed individuals are treated with antidepressants or seen at psychiatric clinics or hospitals.[39] Moreover, antidepressants are prescribed for treatment of conditions other than depression, although depression is the main indication (approximately 80%) for the prescription of selective serotonin reuptake inhibitors.[40,41]

We identified 12 studies[23-28,42-47] with emerging conflicting results regarding use of hormonal contraceptives and the risk for depression (eTable 5 in the Supplement). These studies are reviewed in the eDiscussion in the Supplement.

Conclusions

Use of hormonal contraceptives was associated with subsequent antidepressant use and first diagnosis of depression at a psychiatric hospital among women living in Denmark. Adolescents seemed more vulnerable to this risk than women 20 to 34 years old. Further studies are warranted to examine depression as a potential adverse effect of hormonal contraceptive use.

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